KIDNEY TRANSPLANTATION IN NORTHERN IRELAND

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IT WAS shown by Ullmann as long ago as 1902 that it is possible to transplant the kidney of a dog from its normal site into the neck and renal function will result. He was also able to demonstrate that a kidney taken from another dog, or even from a goat, would also function, but he does not appear to have carried his experiments further. Carrel, working from 1905 to 1910, confirmed Ullmann's report that a kidney could be transplanted from the flank to the neck of the same dog (autotransplant) and would function satisfactorily. He also transplanted a kidney from a dog to a bitch (homotransplant), removing both of the bitch's own kidneys and initially the animal remained well with good kidney function but ultimately the transplanted kidney ceased to function.

Almost another 50 years were to elapse before the first attempt to transplant a kidney into a human being was carried out in 1951 by Scola. This transplant was technically satisfactory, and the kidney produced some urine at first, but, as in the case of Carrel's dogs, the kidney was rejected after a short period. This operation however showed that in the human, as in the dog, it was technically feasible to transplant a kidney.

Much research into the nature of the rejection process was carried out in both this country and the United States by Simonson, Dempster, and Murray, mainly by the study of the behaviour of skin grafts in mice. It had become clear that it ought to be possible to transplant kidneys without fear of rejection, between individuals whose genetic similarity was sufficiently close. The appreciation of this principle led to the first transplantation of a kidney between identical twins in Boston in 1954. This operation was successful and the kidney continued to function for eight years before the glomerulonephritis, which had been the original disease in the patient's own kidneys, attacked the transplanted organ and the patient died of coronary artery disease. Over the next five years attempts to transplant kidneys between identical twins were carried out at a number of centres both in America and Europe. Some of these transplants failed for technical reasons or because of sepsis but in none of them was there any evidence that the kidney was rejected. It is obvious that relatively few patients who reach end stage renal failure will be fortunate enough to have an identical twin who is able and willing to provide a kidney. There was therefore a considerable stimulus to develop a method of preventing rejection of the transplanted organ when kidneys were interchanged between less closely related individuals.

The earliest attempts to prevent the rejection process depended on whole body radiation, and were used in transplants between related individuals. While it was shown as long ago as 1958 that this method would prevent rejection of the kidney, it almost invariable resulted in the death of the patient because of radiation damage to other tissues, especially to bone marrow. These attempts however did demonstrate that it was possible to prevent rejection of the kidneys by recipients who would otherwise not tolerate such a graft.

Further research work on transplantations between dogs by Murray and Calne was directed towards developing a method of suppressing rejection by the use of drugs, at first of the 6-mecaptopurine group. A closely related drug, azathioprine, gave promising results in Calne's dog experiment, and in 1962 it was used for a human patient who received a kidney from a patient recently dead during an open heart operation. The kidney continued to function satisfactorily, despite several rejection crises over the next few months, and sustained the patient for nearly two years, at which point he was given a second graft.

While azathioprine was a major advance over whole body radiation as a method of preventing rejection, it too is toxic to bone marrow and reduces resistance to infection. During the early 60's many other drugs were used for the purpose of damping down the rejection reaction, and in the hope of being able to control this with less hazard to the patient as a whole. Cyclophosphamide, and drugs of the actinomycin group, proved to be even more toxic than azathioprine. It was however discovered that corticosteroids were valuable, probably because of their role as anti-inflammatory agents, and they began to be used in combination with azathioprine, which it was then possible to use in smaller dosage. This became, and still remains, the main method of preventing rejection in patients who have received kidney transplants.

While the combination of azathioprine and steroid has proved a very valuable and therapeutically useful method of preventing rejection of transplanted kidneys it is a kind of blunderbuss therapy, and attempts have been made to produce a more specific attack on the rejection process. The main cell which invades the kidney during the rejection process is the small lymphocyte and attempts have been made to use an antilymphocyte serum for prevention of rejection. It has been possible to produce potent antilymphocyte sera which are effective anti-rejection agents. These sera have recently been purified which removes some of their undesirable side effects. The use of antilymphocyte serum for prevention of rejection has not yet become widespread. This is largely because it is difficult to produce a satisfactory serum and to purify it to the degree of specificity required. Also, there have been reports that patients treated with antilymphocyte serum have developed lymphosarcoma. The possible role of the serum, vis-a-vis the other anti-rejection agents used, in the production of lymphosarcoma in these patients, still remains to be clarified.

At first the results of transplantation of cadaver kidneys were less successful than that achieved by the use of live, related donors, but with increasing experience the results obtained with cadaver donors now closely approach those possible with the use of live donors. In the British Isles, at any rate, kidney grafts taken from live donors have now become rare and the main work depends on the use of cadaver kidneys.

Another factor which has contributed greatly to the successful development of kidney transplantation has been the availability of a satisfactory method of replacing temporarily the function of the kidney by the use of some form of artificial kidney. A patient who has reached end stage renal failure is ill, wasted and usually suffering from an extreme degree of hypertension as well as the biochemical abnormalities resulting from the failure of the kidney to excrete the waste products of metabolism. Such a patient is in no fit state for a major operation, especially one coupled with the use of the toxic drugs required to prevent rejection of the transplanted organ. By the use of the artificial kidney it is possible to return such a patient to a reasonable state of health and maintain him in this state until it is possible to find a kidney suitable for transplantation. Moreover, if the kidney is taken from a cadaver it will not usually function immediately and there will be a period of two to three weeks following the transplant operation before worthwhile function begins. During this period the anoxic damage to the kidney during the period when it was without circulation is repaired. The artificial kidney is used to tide the patient over the period until the transplanted kidney is capable of maintaining him.

So far the problem of matching the kidney to be transplanted to its recipient patient has not been mentioned apart from the question of identical twins. Complex tissue antigens enter into the rejection progress which occurs when a whole organ is transplanted. Our understanding of these is at present still rather rudimentary but sufficient is known to enable some attempt to be made to match kidneys with the recipient patient. The ideal case is that of the identical twin donor where the donor and recipient are furnished with identical sets of antigens. Other less closely related donors share to a lesser or greater extent the same antigens, but also usually have some which differ. Red cell antigens are important in this context and the ordinary rules which apply to blood transfusion have to be observed, but the Rh antigen does not appear to be important. Other tissue antigens are of considerable importance and the growing understanding of these has contributed greatly to the improvement in the results of transplantation between unrelated donors. For the present at any rate, tissue typing is regarded as being similar to lymphocyte typing. Lymphocytes can be typed using antisera by a method analogous to that applied to red cell grouping, though the grouping is more complex and less well understood. It is clearly unlikely that in random unrelated individuals there will be identity of the known tissue groups and some degree of "mismatching" is to be expected. In theory, the less the degree of "mismatch" the easier it ought to be to prevent the rejection reaction following transplantations. The clinical course of the fate of the kidney does not always follow the prediction of the tissue matching but it is thought that this is largely due to imperfections of technique and lack of understanding of the relative importance of different tissue antigens. If the tissue typing of a relatively large panel of patients requiring kidney grafts is known, then the chance of obtaining a good match for the kidneys of any individual donor is greatly enhanced. The modern approach to this problem is to tissue type the potential recipients and record their tissue groups in a computer. When donor kidneys become available the computer selects the best available match in terms of tissue typing. As an additional precaution the recipient's serum is tested directly against lymphocytes taken from the potential

donor to test for preformed recipient antibodies which might lead to early and disastrous hyperacute rejection of the kidney. The computer approach to tissue typing requires that a number of centres pool their respective recipients and their donors. Since the time the kidney can be preserved is limited, other factors besides the "best possible match" have to be taken into consideration.

Position in Northern Ireland 1962–1965

When kidney transplantation began to move out of the realm of pure experiment, in 1962, there was already an established Renal Unit in Northern Ireland. This had been set up in the Belfast City Hospital in 1959 for the purpose of treating renal failure of acute origin where it seemed likely that the patient's own kidney would recover worthwhile function if the patient could be supported for a relatively short period of time. Inevitably some of the patients who were treated with the artificial kidney did not over recover worthwhile kidney function and there were at that time no facilities for the long term support of these patients by repetitive artificial kidney treatment. These circumstances led to an early interest in kidney transplantation.

In 1962 a patient appeared in kidney failure who had an identical twin. The twins were mature adults and the healthy twin was willing and able to donate a kidney to her sister. The transplantation was carried out in Belfast but the transplanted kidney never functioned. Over the next three years a number of patients with end stage renal failure were treated for short spells of time with the artificial kidney and investigated with a view to the possibility of providing a kidney donor from their family Two patients were sent to other centres in Great Great Britain for kidney transplants up to 1964 but neither of these patients survived. It is interesting that neither of them died from rejection, but from technical complications of the transplant procedure.

Position in Northern Ireland 1965–1969

At the beginning of 1965 it became possible to make a more consistent attempt to maintain patients by long term artificial kidney treatment. The technique of preparation of an arteriovenous shunt was developed in Northern Ireland by Mr. Will Hanna and this enabled the same pair of blood vessels to be used for repetitive haemodialysis. The only equipment then available was the coil kidney which had originally been provided for the Renal Unit, and until the end of 1965 it was possible to provide treatment for only one patient with chronic renal failure. However, early in 1965 contact was established with St. Mary's Hospital in London, which was by that time very actively engaged in developing kidney transplantation. Our first patient was sent to St. Mary's in April 1965 and had a kidney transplant at the end of that month. The patient still survives with virtually normal kidney function, the kidney having been taken from an unrelated cadaver donor.

Following this successful transplant a continuing arrangement with first St. Mary's Hospital, and later with Professor Calne's Renal Unit in Cambridge, was developed. When a patient appeared in the Renal Unit here who seemed in every way suitable for a transplant he was presented to one or other of the units involved in transplantation and if they found him acceptable, an arrangement was reached whereby the patient was maintained by long term haemodialysis here until he could be transferred for a space in their transplantation programme. In

due course, usually following several months or even a year or more of haemodialysis here, the patient was transferred to the unit which had accepted him and the transplant was carried out there. After two to three months the patient returned to Northern Ireland and his subsequent anti-rejection therapy and management has been carried out through the Renal Unit here.

Towards the end of 1965 it became possible to support up to four patients on a long-term basis by haemodialysis, largely due to the generosity of Mr. Megaw of the Belfast City Hospital. He permitted the expansion of the Renal Unit into what had previously been a cystoscopy theatre. This room was converted into a two bed dialysis unit and the first Kiil kidneys were acquired. The Kiil kidney is more suitable for the long-term treatment of the chronic patient because it does not require priming blood for each dialysis.

TABLE I

Results of transplantation in Northern Ireland patients

	Patients Transplanted	*Patients Surviving*	*Percentage Survival*
1962–64	3	0	0
1965	2	2	100
1966	3	3	100
1967	2	2	100
1968	7	2	28
1969	5	4	80
1970	7	7	100
Total	29	20	70

The work of maintenance haemodialysis with a view to transplantation therefore continued in the main block of the Belfast City Hospital until the summer of 1968 when the new Renal Unit behind the Ava block became available. The results in terms of transplantation are shown in Table 1. All patients shown as surviving in the Table have good kidney function, most with a creatinine clearance above 50 ml/min. They are treated with aziathioprine and steroids only. They have a normal diet and fluid intake and most do not require any hypotensive therapy. They are all capable of useful employment.

It is of considerable interest that all the patients who have survived have received their kidneys from cadaver donors. In 1968 two patients received kidneys from parent donors but neither patient survived. In one of these patients the kidney was rejected acutely despite the fact that tissue typing suggested that the outlook for the kidney was good. The other patient died from fulminant chickenpox.

The tissue typing results are known of the patients transplanted from 1968 onwards but until the last patient transplanted in 1969, the tissue typing was not known in advance of the transplantation, with the exception of the two live donor cases already mentioned.

The provision of the new Renal Unit at Belfast City Hospital, with its special ventilation and its own theatre, made it possible to commence kidney transplantation here. In preparation for this the team connected with the Renal Unit was strengthened by the addition of the part-time services of two surgeons, an immunologist and two anaesthetists. The facilities for long-term maintenance by haemodialysis have not been greatly increased by this building and it is possible to support only six patients at any one time. However, a 10-bed chronic dialysis unit is in the process of building and should be ready for use by the spring of 1971. The maximum number of transplants that could be managed with the present facilities is about twelve per annum and this number would depend on all circumstances being favourable, including the appearance of suitable donors at the appropriate time when patients were ready to receive them.

In November 1968 the first transplant was carried out in the Renal Unit. The operation and the post-operative course were smooth and complicated only by the expected period of tubular necrosis during which the patient was maintained by artificial kidney treatment. By three weeks the patient became self supporting and was discharged from hospital. However, the retrospective tissue typing showed that the kidney was a poor match for the patient and it was predicted that the kidney would be rejected within a relatively short space of time, and indeed this happened after 14 weeks. Eleven further transplants have been carried out since then. There have been a number of technical complications but despite these the eleven patients remain alive and all have satisfactory kidney function. The earlier transplants have shown a slow improvement in kidney function and the two earliest ones now have creatinine clearance of over 80 ml. per minute.

The last patient from Northern Ireland to be transplanted elsewhere was in January 1969. After 17 months the patient died following a severe rejection of the kidney.

While the current results using cadaver kidneys have produced very encouraging results it must be remembered that the patients dialysed and transplanted account for only a small proportion of those patients who need it. A survey carried out in Northern Ireland has shown that in 1968 some 50 patients aged between 15 and 55 reached end-stage renal failure and as far as can be determined these patients were medically suitable for dialysis and transplantation. There were an additional 57 patients within this age group who reached renal failure but in whom there appeared to be some medical contra-indication to this form of treatment.

When the 10-bed chronic dialysis unit was planned during 1966/67 the emphasis in treatment for end-stage renal failure was directed largely towards chronic dialysis rather than towards transplantation. It was planned to augment the hospital dialysis service by training patients for home dialysis. The 10-bed unit would provide for hospital dialysis for up to 30 patients and it could train up to 12 patients for home dialysis per annum. Therefore once the unit was initially filled, which to judge from the figure mentioned above would be well within the first year of operation of the unit, it would become possible to treat only 12 new patients going into home dialysis per annum, plus possibly 12 patients to be transplanted within the existing service. The service would therefore be able to treat only about half the new patients appearing each year.

The logical solution for this problem would be to develop the transplantation service to a stage where approximately 50 transplants could be carried out per annum. This would require a considerable outlay in salaries for additional staff, but appears to be possible. As the cost of the proposed provisions of home dialysis for 12 patients per annum is very large, this could be done out of this sum, still allowing for home dialysis treatment for the few patients who would prove unsuitable for transplantation, and show a substantial saving in cost. An estimate of the possible saving over a five year period of the cost of transplantation as opposed to the provision of home dialysis for 12 new patients per annum would be of the order of £168,000.

In addition to the advantage of providing treatment for most, if not all, patients who would require it, an increase in the transplant service to this level would provide a much better form of treatment for the patients. The patient who has received a successful transplant is free from the necessity of machine treatment two or three times a week, from the hazards attached to the repetitive use of vessels for dialysis, and from the restrictions of diet and fluid intake entailed. In addition patients who have been transplanted achieve a much better level of health than is possible by repetitive dialysis.

A major problem to be faced in the development of transplantation to this level is the supply of donor kidneys. We in Northern Ireland, in common with all other Renal Units involved in transplantation, are faced with an apparent shortage of suitable kidney donors. It is therefore pertinent to look at the problem from this point of view. As the work here and in most centres in Great Britain depends on the supply of cadaver donors it is important to consider whether there is in fact a real shortage of of donor kidneys or whether this may be only apparent.

Kidneys for use for transplantation must be removed and chilled within one hour of the death of the donor so that the donor must die in hospital. The cause of death should not have been associated with infection, malignant disease or prolonged low blood pressure, the last of which would lead to anoxic damage of the graft. The age of the donor patient is of less importance and kidneys can be taken and grafted successfully from patients about the age of eight up to 60 or more years. Most suitable donors die from accidents, especially from head injuries, primary brain tumours which do not tend to spread outside the skull, subarachnoid haemorrhage, cerebro-vascular damage to the brain, or possibly from coronary thrombosis or during cardiac surgery. Patients known to have proteinuria, hypertension or elevated blood urea prior to death would not be acceptable.

There is little information available about the potential numbers of such patients, but Friedberg, Larsen and Larsen (1970) reported that in their 900-bed hospital in Copenhagen there were 44 acceptable cadaveric kidney donors in one year, as judged by a survey of autopsies. Their hospital does not include a neurosurgical unit. Patients who are brought in dead or who die following accidents are dealt with separately by the Institute of Forensic Medicine and are not included in their figures. As their criteria for the selection of donors were rather strict and patients dying from accidents were excluded, their figures are probably an underestimation of the number of available donors.

In theory each potential donor enables two patients with end-stage renal failure

to have transplants. We would therefore appear to require 25 donors per annum to enable us to treat our 50 potential patients. This however is likely to be an underestimate of the number of donors required as we have found in our limited experience that a surprising number of kidneys are unsuitable from a surgical point of view because of multiple vessels. Our probable need of donors is more likely to be 35 than 25 per annum. Judging from the Copenhagen survey, this number of donors ought to be available within the Belfast hospitals.

Although the kidney must be removed and chilled within one hour of death it can be kept in a cold condition for a period of 10 to 12 hours without significant further deterioration. This space of time is sufficient for tissue typing to be carried out and for kidneys to be removed from one centre to another if no suitable recipient is available locally. As this aspect of the service is developed it will enable kidneys to be used for transplantation which would otherwise be wasted. This kind of exchange is already taking place and on five occasions we have sent kidneys across to London or elsewhere and two of our patients have received transplants of kidneys obtained from other centres.

Ethics and the Law

The present conditions for taking kidneys for transplant are laid down by The Human Tissue Act of 1961. If an individual's wishes as to the disposal of his own body are known these have to be respected. If the deceased's wishes are not known, permission for removal of organs for transplantation can be given by relatives. If after "undertaking such reasonable enquiry as may be practicable" the relatives cannot be contacted, then the person in charge of the body can give permission. In practice most transplant centres use kidneys only when a relative has given permission.

The need to obtain donor organs must not be allowed in any way to influence the treatment of the patient who becomes the donor. Members of the transplantation team must not in any way be involved in the treatment of the potential donor and no unnecessary investigations are performed with the exception of the removal of a small volume of blood for red cell grouping and tissue typing. The Coroner's permission must be obtained for the removal of the kidney. In practice most coroners are sympathetic to the needs of transplantation and will usually allow removal of organs for transplantation unless this would prevent them from establishing the cause of death.

Before the organs are removed death must be pronounced to have taken place by two doctors who are not members of the transplantation team, one of whom must be qualified at least five years. Thus it can be seen that great care is taken that the possibility of an organ becoming available for transplantation will not in any way run counter to the normal medical care of the potential donor.

Kidneys for grafting are therefore taken from dead patients under these safeguards and it is difficult to see how there can be any ethical objection to the transplantation of cadaver kidneys. The inevitable tragedy to the family of the loss of a near and dear relative cannot be made worse by removal of a kidney for transplantation. Indeed the use of the kidneys for transplantation may provide some small measure of comfort in tragic circumstances. As Professor Calne has said, "Most of us would make every endeavour to save a man drowning, many

would risk life and limb in the attempt. To donate one's organs after death is a similar act of charity which involves no risk at all yet can provide another human being with the gift of life."

The work described here has been carried out by the united efforts of many people, too numerous to mention individually. We are greatly indebted to nursing staff, technicians, registrars and research fellows and to all branches of the laboratory service. Without all these and the help of consultant colleagues who provided cadaver kidneys, it would be impossible to function as a Renal Unit.

We are especially grateful to colleagues in St. Mary's Hospital, London and in Addenbrooke's Hospital, Cambridge, who carried out kidney transplants for our earlier patients.

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